Management of Patent Ductus Arteriosus in Preterm Patients Who Were Given Surfactant

Patent Ductus Arteriosus Management

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Abstract

Aim: Respiratory distress syndrome (RDS) and perinatal asphyxia are known to be risk factors in hemodynamically significant Patent Ductus Arteriosus (hs-PDA). In this study, we aimed to reveal scientific data in respiratory distressed preterm infants in the light of the current literature and to discuss the management of PDA in babies born at 33d weeks of gestation and up to 33d weeks which we have treated and followed in our unit. Materials and Methods: The medical records of premature infants treated at Necmettin Erbakan University Neonatal Intensive Care Unit (NICU) between January 2016 and January 2019 were retrospectively evaluated. Results: Between January 2016 and January 2019, 476 patients born prior to 33d gestational weeks were admitted to our unit.. PDA was detected in 149 of these patients because of RDS due to the surfactants. In 112 (75.1%) of these patients, the PDA closed spontaneously within the first week of life. Thirty-seven (24.8%) patients developed hs-PDA. The incidence of premature retinopathy (ROP), bronchopulmonary dysplasia (BPD), and late neonatal sepsis morbidity was significantly elevated during the hospitalization (p=0.05, p=0.01, p=0.06). Invasive mechanical ventilation, non-invasive mechanical ventilation, and free oxygen requirement times were found to be longer (p= 0.0001, p= 0.004, p= 0.014). Complete enteral nutrition and discharge times were longer in the treated group (p= 0.03, p= 0.002). We identified the presence of Small for Gestational Age (SGA) (r = 0.30 p = 0.04) and low birth weight (r = 0.99 p = 0.02) in logistic regression analysis of the factors affecting the PDA as meaningful results. Discussion: The presence of hs-PDA in infants with RDS is directly proportional to the birth week and weight, the presence of SGA reduces the frequency of hs-PDAs, the presence of hs-PDA is associated with ROP, BPD, and late sepsis. The presence of hs-PDA has been found to be correlated with prolonged respiratory support and delayed discharge.

Keywords

Preterm; Patent Ductus Arteriosus; Respiratory Distress Syndrome; Surfactant

Introduction

Ductus arteriosus (DA) is an arterial site that is located between the pulmonary artery and aorta in fetal life, allowing blood to bypass the non-airborne lungs and enter the systemic circulation. The closure process, which constitutes the basis of the vascular passage of the postpartum-separated arteriovenous circulation pattern in the first 24 hours, occurs functionally with luminal narrowing as a result of contraction of the flat muscle in the structure of the ductus [1]. In a few weeks, permanent closure occurs due to fibrosis and the degeneration of subintimal layers [2]. When the ductus of the postpartum term babies are closed smoothly, the DA tissue in the premature baby cannot be closed due to its structural properties, and the failure of this closure exceeding 72 hours is referred to as the Patent Ductus Arteriosus (PDA). Due to hemodynamic instability, pulmonary edema and bleeding are associated with significant morbidities such as bronchopulmonary dysplasia (BPD), intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), feed intolerance and premature retinopathy (ROP) [3].

Patent DA frequency is inversely proportional to gestational week and birth weight. In the studies on prematurity, the rates vary between 29-80%. In a study published in 2015, 182 thousand premature infants (< 32 weeks) born between 2003 and 2009 in the USA were examined. The frequency of PDA was found to be 27% in infants born prior to 28 weeks and 11% at 29-32 weeks. In 2003, the prematurity rate of PDA in infants born up to 32 weeks was 14%, and in 2009, this rate increased to 21% [4]. This increase has been experienced in both < 28 weeks infants and 29-32 weeks infants and is too high to be explained by technological developments.

Despite this, the effect of treating PDA in the last 10 years has become controversial, with less medical and surgical treatment and a conservative approach coming to the fore [5].

Respiratory distress syndrome and perinatal asphyxia are known to be risk factors in hs-PDA. In this study, we aimed to reveal scientific data in respiratory distressed preterm infants in the light of the current literature and to discuss the management of PDA in babies born at 33 weeks and prior to 33 weeks which we have treated and followed in our unit.

Material and Methods

The medical records of premature infants treated at Necmettin Erbakan University Neonatal Intensive Care Unit (NICU) between January 2016 and January 2019 were retrospectively evaluated.

Ethics Committee approval for this study was obtained from Necmettin Erbakan University with the Ethics Committee decision number of 2019/1729.

Patients who were born at Necmettin Erbakan University, which were given surfactant from the gestational age ≤ 33, or transferred within 72 hours, were included in the study with echocardiography within 72-96 hours. Patients with congenital anomalies and complex cardiac defects without PDA were excluded from the study. Demographic details including, gestational age, birth weight, maternal age, maternal problems, Apgar scores, chorioamnionitis, surfactant dose repetition, antenatal steroid use, invasive mechanical ventilation time, non-invasive mechanical ventilation time , free oxygen need time, BPD, ROP,

NEC, IVH, late sepsis, time to enter full enteral feeding, time of discharge, mortality and the presence or treatment of PDA were collected.

Echocardiography was performed within the first 72-96 hours of life in all preterms admitted to NICU by the same pediatric cardiologist. Hemodynamically significant PDA (hs-PDA) was defined with the echocardiographic evidence of ductal lumen over 1.5 mm and left atrium diameter (LA)/aortic root diameter (AO) ratio over 1.4 and documentation of left to right shunt [6]. Patients with hemodynamically insignificant PDA (hiPDA) were not given any medical treatment but were followed up echocardiographically for ductal closure.

Hemodynamically significant medical treatment for PDA, one dose of 10 mg/kg Ibuprofen IV for the 1st day, on the second and 3rd days, a single dose of 5 mg/kg was given duringthe day. On the 4th day of IV treatment, closure of ductus arteriosus was re-evaluated by echocardiography to decide on the requirement for an additional course of ibuprofen. For patients who failed the first oral ibuprofen course, the therapy was changed to IV ibuprofen for up to two courses. In the case of hs-PDA, despite two curing treatments, surgical ligation was given.

Respiratory distress syndrome (RDS) was diagnosed clinically with early respiratory distress manifested by grunting, cyanosis, retractions, and tachypnea. The diagnosis was confirmed byblood gas analysis and chest X-ray with a classical "ground glass" appearance and air bronchograms. Surfactant therapy was administered in accordance with the European Consensus Guidelines and the American Academy of Pediatrics [7]. Surfactant therapy was applied prophylactically or as a rescue therapy to reduce the risk of neonatal mortality [8]. BPD was administered as needed for oxygen at 36 weeks postmenstrual age or at the time of discharge or transfer to Level 2 NICUs [9]; NEC ≥ Stage 2 [10]; and severe brain injury, which included intraventricular hemorrhage (IVH) ≥ Stage 3.

Statistical Analyses

The numerical variables are defined by mean, standard deviation, median and IQR statistics. Categorical variables were given as numbers and percentages. A t-test was used to compare numerical variables. The Chi-squared or Fisher's Exact tests were used for categorical variables. The analyses were made using the SAS University Edition 9.4 program. $P < 0.05$ was considered significant. Logistic regression analysis was performed to find the risk factors of PDA.

Results

Between January 2016 and January 2019, 476 patients born prior to 33 gestational weeks were admitted to our unit. PDA was detected in 149 of these patients because of RDS due to the surfactants. In 112 (75.1%) of these patients, the PDA closed spontaneously within the first week of life. Thirty-seven (24.8%) patients developed hs-PDA. In the hs-PDA group, the birth week (28.26 ± 3.3; 29.5 ± 3.36; P= 0046) and the birth weight (1100.8 ± 457.9; 1313.4 ± 663; P= 0.07) were found to be low compared to the other group. The comparison of the characteristics of the two groups is given in Table 1.

The incidence of ROP, BPD, and late neonatal sepsis morbidity was significantly elevated during hospitalization (p= 0.05; p= 0.01; p= 0.06). Invasive mechanical ventilation, non-invasive

Table 1. Features of groups with PDA and without PDA treatment

Characteristics	nHS-PDA (n=112)	HS-PDA (n=37)	P value
GA (weeks), mean (SD)	29.5±3.36	28.26±3.3	0.046
BW (grams), mean (SD)	1313.4±663	1100.8±457.9	0.07
SGA , n (%)	23 (20.5)	4(10.8)	0.18
Age of mother, mean (SD)	28.6±5.7	30.0±6.3	0.22
Apgar at 5 min, n (%)	5.6±1.6	5.8±1.2	0.3
Apgar at 1 min, n (%)	4.4±1.8	4.37±1.6	0.8
Maternal gestational diabetes n (%)	7 (6.25)	3(8.11)	0.7
Maternal preeclampsia, n (%)	25(22.3)	8(21.6)	1
Chorioamnionitis, n (%)	14(12.5)	4(10.8)	1
Surfactant dose repetition, n (%)	31(27.68)	15(40.5)	0.15
Antenatal steroid use, n (%)	60(53.57)	20(54.05)	1

Table 2. Comparison of secondary outcomes of patients with and without PDA treatment

Outcome	nHS-PDA (n=112)	HS-PDA (n=37)	P value
Invasive mechanical ventilation time (day), mean (SD)	4.54±8.1	12.7±13.0	<.0001
Non- invasive mechanical ventilation time (day), mean (SD)	7.17±10.3	13.7±16.4	0.004
Free oxygen need time (day), mean (SD)	10.3±15.2	17.8±18.7	0.014
BPD, n (%)	13(11.6)	9(24.3)	0.05
ROP, n (%)	18(16.07)	13(35.1)	0.01
NEC, n (%)	9(8.26)	5(13.5)	0.34
IVH, n (%)	21(19.8)	11(29.7)	0.25
Sepsis, n(%)	26(23.2)	18(48.6)	0.006
Time to enter full enteral feeding (day), mean (SD)	14.6±9.2	18.9±9.5	0.03
Time of discharge (day), mean (SD)	43.3±26.5	62.8±35.3	0.002
Mortality, n (%)	22(19.6)	8(21.6)	0.8

Table 3. Comparison of PDA treatment groups with respect to features and secondary outcomes

Characteristics	Medical only (n=37)	Both medical and surgical (n=5)	P value
GA (weeks), mean (SD)	28.0±2.9	29.0±4.6	0.63
BW (grams), mean (SD)	1111.1±460.2	1047.5±484.5	0.77
Age of mother, mean (SD)	29.7±6.38	31.5±6.7	0.54
Apgar at 5 min < 5, n (%)	6.0±1.3	5.3±0.8	0.13
Apgar at 1 min < 5, n (%)	4.4±1.7	4.16±0.75	0.57
Surfactant dose repetition, n (%)	12(38.7)	3(50)	0.66
Antenatal steroid use, n (%)	17(54.8)	3(50)	1
BPD, n (%)	8(25.8)	1(16.6)	1
ROP, n (%)	10(32.2)	3(50)	0.64
NEC, n (%)	5(16.1)	0(0)	0.56
IVH , n (%)	9(29.0)	2(33.3)	1
Time to enter full enteral feeding (day),mean(SD)	18.3±9.7	21.0±9.5	0.56
Mortality, n (%)	8(25.8)	0	0.3

mechanical ventilation, and free oxygen requirement times were found to be longer (p= 0.0001; p= 0.004; p= 0.014). Complete enteral nutrition and discharge times were longer in the treated group (p= 0.03; p= 0.002). There was no significant difference in terms of mortality, NEC, and IVH (Table 2).

We identified the presence of SGA (r = 0.30; p = 0.04) and low birth weight (r = 0.99; p = 0.02) in logistic regression analysis of the factors affecting the PDA as meaningful results.

There was no significant difference in the comparison between the different treatment groups in terms of characteristics and secondary outcomes (Table 3).

Discussion

Inability to close the ductus in preterm infants is explained by a number of reasons, such as genetic factors, lack of vasa vasorum for nutrition due to its thin walls, low rate of Ca++ sensitivity increased by oxygen in muscular smooth muscle cells, slow pace of the decrease in circulating prostaglandins levels after childbirth, increased susceptibility to nitric oxide and endothelin-1 [11]. Hemodynamic significance is inversely associated with birth week of the infant with PDA and birth weight. Although the majority of the PDAs were closed at the end of the first week for the preterms born at gestational weeks ≥ 28, however, in those born prior to 28 weeks, the ductus was reported to be open for numerous weeks in50-70% of preterms [12]. In a study of 280 Very-low-birth-weight infants with patent DA, in 237 of which their ductus was conservatively followed, spontaneous bleeding times were observed to be significantly shorter in those born at >28 weeks and >1250 gr babies than in infants born prior to 28 weeks and < 1250 gr [13]. In our study, which included preterms under 33 weeks, the hs-PDA was statistically significantly lower than the non-hsPDA group, and 86.1% of these infants with a gestational age 28 weeks and less. However, the hs-PDA group was seen to have lower birth weights compared to the non-hsPDA group.

In the literature, there are various data on the association between the use of antenatal corticosteroids and the incidence of PDA [14,15]. In a multicenter study, which included 6437 infants born between 24-34 gestational weeks, it was observed that PDA did not differ meaningfully between the group that received antenatal steroid injectionand the group that did not [16]. In our study, the relationship between the application of antenatal corticosteroids and hs-PDA was not found.

The presence of SGA in preterm infants is known as an additional main risk factor for mortality and morbidity [17]. While some studies detected a correlation related to patent ductus arteriosus and SGA [18], there are also those who claim otherwise and that it reduces the risk of seeing PDA [19]. A multicentric study by Boghossian et al. on 156 587 babies at 22-29 birth weeks found that in babies with SGA aged between 23-24 weeks the risk of PDA decreases and that infants who were born between 26-29 weeks had a general increase of PDA [20]. In our study, there was no significant difference in SGA between the hs-PDA and non-hs-PDA groups. Nevertheless, we found that through logistic regression the factors affecting PDA reduced with the presence of SGA.

The average maternal age was similar among groups. We have seen that risk factors such as preeclampsia, gestational diabetes, and chorioamnionitis do not differ significantly between the two groups. Rastogi et al. compared similar risk factors in NICU infants whose mothers were obese or not and found that gestational diabetes increased PDA by 3.36 times, while the pre-eclectic was unrelated to PDA [21].

Surfactant used in RDS reduces lung vascular resistance improving lung parenchyma disease. However, it increases the risk of the shunt from left to right. Kumar and colleagues showed that the risk of hs-PDA is increased in infants with RDS, which

is more likely to increase the incidence of therapeutic interventions to close the ductus with larger transducer diameters [22]. We have not done such a comparison because we selected our study group from patients with RDS that we treated with surfactants. However, there was no significant difference between the two groups regarding the relationship between weight and RDS dose recurrence. Based on this, we can say that the RDS intensity is not directly related to hs-PDA.

Hemodynamic significant-PDAs, decrease in systemic blood pressure and decreased flow to the organs, increased pulmonary blood pressures and flows, pulmonary edema, decreased lung compliance causes significant hemodynamic results [23]. However, it remains unclear whether the hs-PDA is causing a mortality increase and/or any specific neonatal illness. Although there is no evidence of a direct cause and effect relationship, there has been a significant correlation between major PDA shunt volume and morbidity, such as BPD. For this reason, there are various results in many studies in the literature that reveal the relationship between mortality and morbidity inthe presence of hs-PDA. Sellmer et al. found that on the 3rd day, the rate of mortality, BPD, and IVH increased in non-preterm groups born at 28 weeks with hs-PDA [24]. According to the scoring systems based on echocardiological measurements before treatment, Sehgal et al. showed high BPD growth rate in infants with high scores [25]. Sung et al. on the contrary, did not associate hs-PDA with mortality and morbidity in 23-28 weeks excessive preterm infants [26]. In our study, we found that the BPD and ROP ratio is significantly higher in the hs-PDA group. In addition, late neonatal sepsis occurred more in patients of this group. In our opinion, patients in the hs-PDA group have a longer period of invasive, non-invasive mechanical ventilation, and free oxygen requirements than the other group, which explains the increase in the rate of ROP and late neonatal sepsis. Another dimension of the relationship with late neonatal sepsis can be explained by the effects of the release of cytokine during sepsis as it was emphasized in the work of Terek et al.[15]. A hemodynamically significant-PDA, by virtue of 'stealing' blood from the descending aorta to the pulmonary circulation, is thought to result in a chronic state of relative gut hypoperfusion. In addition, a commonly used agent in the medical treatment of PDA, indomethacin, also shows a vasoconstrictor effect on the mesenteric artery. Although it is not proven with randomized controlled trials, it is a fact that both hs-PDA and indomethacin therapy are given a break in full enteral nutrition, in consideration of the possible relationship with NEC [27]. Unfortunately, this process extends the passage of infants to full enteral nutrition. In randomized controlled studies by Clyman et al., the continuation of trophic nutrition during the treatment of PDAs with nonsteroidal anti-inflammatory drugs reduces the time of reaching full enteral nutrition compared to unfed neonates [28]. We have seen that even though we stop feeding in the patients we treat, this leads to greater intolerance and the duration of the transition to full enteral feeding is longer when nutrition is increased slow. Multifactor reasons such as long respiratory support, late sepsis, and late transition to full enteral nutrition cause longer hospitalization periods. We observed a significant difference between both groups in terms of mortality.

In recent years, the approach to hs-PDA has begun to change from medical and surgical treatment to conservative treatment. The treatment decision is a very controversial process. In our clinic, we treated patients with hemodynamics that deteriorated and observed the systemic effects of hs-PDA. There were no differences in the characteristics and secondary outcomes between surgical and medical-treatment groups. Similarly, Gersony et al. compared the clinical outcomes of the symptomatic patients who underwent surgical ligation with medical treatment and revealed that there was no difference in mortality, BPD, NEK, ROP, IVH, or sepsis [29]. However, somestudies report increased ROP, BPD, and neurosensory disorders in patients with direct surgical ligation. According to the common conclusion of all these studies, surgical intervention is preferred only if the medical treatment is contraindicated or there has been no response to treatment. In our study as well, the number of patients who have undergone surgery is very low which supports us not to be aggressive in interfering with the ductus and to adopt a management policy that runs parallel to current approaches. Hence, in centers where the surgical practice is not good enough, it becomes inevitable to struggle with a number of postoperative complications. However, the early routine pharmacological treatment of PDA-TOLARE, which was recently published, compared the conservative approach that treated only when predetermined respiratory and hemodynamic recovery criteria were met. The authors found that early routine treatment of medium and large PDAs at the end of the first week in infants born during the 28th gestational week does not reduce the presence of PDA ligations or PDAs during discharge, does not improve any of the predetermined secondary results and delays full enteral nutrition. Furthermore, they found that it increases the risk of late-onset sepsis and death in infants ≥ 26 week gestation [30].

Conclusion

The presence of hs-PDA in infants with RDS is directly proportional to the birth week and weight, the presence of SGA reduces the frequency of hs-PDAs, the presence of hs-PDA is associated with ROP, BPD, and late sepsis. The presence of hs-PDA has been found to be correlated with prolonged respiratory support and delayed discharge. The decision for surgery should be conservative. The treatment decision of patients who do not have a hemodynamic disorder and clinical symptoms should be individualized.

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